

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	Atty Docket No.	TJCZ-00101-NUS
Hesheng Zhang	Art Unit:	1625
US Serial No.:	Examiner:	CHANG, CELIA C
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Confirmation No. 3461		
For: Novel process for preparing donepezil and its derivatives		

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
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DECLARATION UNDER 37 CFR 1.132

SIR:

Hesheng ZHANG declares as follows:

1. I am the sole inventor of an invention on which the above-referenced application was filed.

2. I have obtained my master degree in organic synthesis from Nankai University in 1987 and my doctoral degree in medicinal chemistry from Rutgers, The State University of New Jersey, in 1999.

3. I am employed at Tianjin Hemay Bio-Tech Co., LTD in the position of General Manager and have been employed in that position since 2002.

4. I am intimately familiar with donepezil and its derivatives. I am considered a person of ordinary skill in the relevant art.

5. The above-referenced application relates to a novel process for preparing donepezil and its derivatives.

6. The novel process for preparing donepezil and its derivatives claimed in the above-referenced Application were not known prior to our invention.

7. My application teaches a process for preparing donepezil and its derivatives:

8. A skilled person in the art such as myself would not have arrived at the process for preparing donepezil and its derivatives as claimed in the pending claims after considering the reference teachings of Lensky (U.S. Pat. 5,606,064), Devries '584 (WO 97/22584), Devries et al. (U.S. Pat. No. 5,916,902) ("Devries '902"), either alone or in combination.

9. It is well-known to a skilled person that p-toluene sulfonic acid plays the role of a catalyst in the reaction of 5,6-dimethoxy-indan-1-one with pyridine-4-carboxaldehyde to produce 5,6-dimethoxy-2-(pyridine-4-yl)methylene-indan-1-one. At the time the invention was made, a person with ordinary skill in the art would not have known that p-toluene sulfonic acid reacts with 5,6-dimethoxy-indan-1-one and pyridine-4-carboxaldehyde to produce a tosylate salt. To the best of Applicant's knowledge, the compounds of formula (III) and formula (IV) have been first prepared and fully characterized by Applicant (and their CAS numbers were first assigned in connection with Applicant's invention).

10. Lensky recites reacting 5,6-dimethoxy-indan-1-one with pyridine-4-carboxaldehyde in the presence of p-toluene sulfonic acid to obtain a solid or a precipitate, then the solid or precipitate is stirred with 10% aqueous sodium carbonate solution to obtain 5,6-dimethoxy-2-(pyridine-4-yl)methylene-indan-1-one. Any 4-((5,6-dimethoxy-1-oxo-1H-inden-2(3H)-ylidene)methyl)pyridinium 4-methylbenzenesulfonate formed in the processes of Lensky is basified using 10% aqueous sodium carbonate solution and immediately converts to the free 5,6-dimethoxy-2-(pyridine-4-ylmethylene)-2,3-dihydro-1H-inden-1-one. A skilled artisan, such as myself, would not have known that 4-((5,6-dimethoxy-1-oxo-1H-

inden-2(3H)-ylidene)methyl)pyridinium 4-methylbenzenesulfonate would form in the processes of Lensky. After reading Lensky, a skilled artisan would not have known that it is beneficial to hydrogenate 4-((5,6-dimethoxy-1-oxo-1H-inden-2(3H)-ylidene)methyl)pyridinium 4-methylbenzenesulfonate directly because a skilled artisan would not have known the property of this intermediate, particularly the reducibility of the C=C bond and the pyridinyl ring of this intermediate at room temperature and at a pressure of one atmosphere of H₂ via a single-step hydrogenation.

11. The differences between the present process and Devries '584 are large. In Devries '584, hydrogenation occurs at the stage of 3-pyridin-4-ylpropen-2-oic acid rather than as in Applicant's process at the stage of 4-((5,6-dimethoxy-1-oxo-1H-inden-2(3H)-ylidene)methyl)pyridinium 4-methylbenzenesulfonate. 3-pyridin-4-ylpropen-2-oic acid is much different from 4-((5,6-dimethoxy-1-oxo-1H-inden-2(3H)-ylidene)methyl)pyridinium 4-methylbenzenesulfonate. A skilled artisan, such as myself, would not be able to conclude after reading Devries '584 that 4-((5,6-dimethoxy-1-oxo-1H-inden-2(3H)-ylidene)methyl)pyridinium 4-methylbenzenesulfonate could be successfully hydrogenated in a single step.

12. By hydrogenating 4-((5,6-dimethoxy-1-oxo-1H-inden-2(3H)-ylidene)methyl)pyridinium 4-methylbenzenesulfonate directly, the method of the present application is much simpler and more environmentally friendly than the methods described in the cited references.

13. The yield of donepezil according to the process as claimed is unexpectedly much higher than that disclosed in the cited references. Lensky's yield for producing donepezil is less than 58%. Also, the scientists of Eisai Co. repeated the process of Lensky (U.S. Pat. 6,252,081), and found that the yield of the last hydrogenation step (the conversion of 1-benzyl-4-((5,6-dimethoxy-1-oxo-1H-inden-2(3H)-ylidene)methyl)pyridinium bromide to 2-((1-benzylpiperidin-4-yl)methyl)-5,6-dimethoxy-2,3-dihydro-1H-inden-1-one) is only 38% and that this yield is even not reproducible. With respect to Devries '584, the yield for

producing donepezil is only about 19% due to the complex steps involved. In contrast, the yield of donepezil according to Applicant's process is as high as 85%. This result is unexpected and superior.

14. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the above-referenced application or any patent issuing thereon.

A handwritten signature in black ink, enclosed within a large, hand-drawn oval. The signature appears to be 'Hesheng Zhang' in a cursive style.

Hesheng Zhang

Date: December 15, 2011